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EXAMINER
KWON, BRIAN YONG S

ART UNIT	PAPER NUMBER
1614	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/051,770	Applicant(s) GLICK ET AL.	
	Examiner Brian S Kwon	Art Unit 1614	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *1-20, 27, 29-31, 35-45 and 47-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-26,28,32-34 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants Response to Election/Restrictions Requirement

1. Applicants election with traverse the Group I, claims 21-34 and 45-46, along with 18-methoxycoronaridine as the first α3β4 nicotinic receptor antagonist and dextromethorphan as the second α3β4 nicotinic receptor antagonist (without traverse) is acknowledged. Claims 21-26, 28, 32-34 and 46 read on the elected species.

With respect to the Examiner's restriction between Group I and II (further II(a) and II(b)), Applicants traverse the restriction requirement on the grounds that there would be no burden in searching the invention of Group I and Group II since they are related to one another and would necessarily require common areas of search and consideration (due to their same classification). This argument is not persuasive, as claimed invention would be distinctive, each from the other for the reason of the record. The claimed invention in Group II, drawn to a process of treating addiction disorders can be practiced with another materially different products such as azetidines, tachykinin antagonists, monoamine oxidase inhibitor, selegiline, pramipexole and etc... Therefore, Invention in Group I is distinct from Group II invention.

With respect to the Examiner's restriction between Group III and Group I or Group II invention, Applicants traverse the restriction requirement on the grounds that there is no acceptable rationale for such restriction. This argument is not persuasive, as claimed invention would be distinctive, each from the other for their different classification, invention III (classified in class 435, subclass 7.8, 334) and Invention I or II (classified in class 514, subclass 282). Therefore, the search required in Group III is not required for Group I or II.

With respect to the Examiner's restriction between Group II(a) and Group II(b), Applicants traverse the restriction requirement on the grounds that there is no rationale provided for such restriction. This argument is found persuasive. Therefore, the restriction between Group II(a) and Group II(b) is withdrawn.

Although the Examiner withdraws the restriction requirement between Group II(a) and Group II(b), the Examiner maintains that the restriction requirement among Group I-III is still deemed proper, and made Final. Claims 1-20, 27, 29-31, 35-45 and 47-50 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims, the requirement having been traversed in Paper No. 8.

2. Claims 21-26, 28, 32-34, 46 are currently pending for the prosecution on the merits.

Information Disclosure Statement

3. Enclosed is an initialed copy of PTO 1449 which has been considered for your records, Application No. 10/051770.

Priority

4. Applicant's claim for benefit of 60/264,742 filed on 01/29/2001 (domestic priority) under 35 U.S.C. 119(e) is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 21-23 and 32-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mecamylaine, 18-methoxycoronaridine, bupropion, dextromethorphan and dextrorphan, does not reasonably provide enabling for α3β4 nicotinic receptor antagonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention relates to a method of composition comprising first α3β4 nicotinic receptor antagonist and second α3β4 nicotinic receptor antagonist, wherein (a) when the first α3β4 nicotinic receptor antagonist is dextromethorphan, the second α3β4 nicotinic receptor antagonist is not dextrorphan; (b) when the first α3β4 nicotinic receptor antagonist is dextrorphan, the second α3β4 nicotinic receptor antagonist is not dextromethorphan; (c) when

the first α3β4 nicotinic receptor antagonist is dextromethorphan, dextrorphan, or mecamylamine, the second α3β4 nicotinic receptor antagonist is not bupropion; and (d) when the first α3β4 nicotinic receptor antagonist is bupropion, the second α3β4 nicotinic receptor antagonist is not dextromethorphan, dextrorphan or mecamylamine.

(2) The state of the prior art

The compounds of the inventions are α3β4 nicotinic receptor antagonists.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5(BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 9999 F.2d 1577, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir.

1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of compounds having α3β4 nicotinic receptor antagonist prior to filling of the instant invention was an unpredictable art.

(5) The breadth of the claims

The instant specification (page 6, lines 14-17) discloses that "α3β4 nicotinic receptor antagonist" means a compound that directly or indirectly blocks or otherwise reduces the activity of an α3β4 nicotinic receptor antagonist. The scope of instant invention encompasses specific α3β4 antagonists, non-specific α3β4 antagonists, partial antagonists (mixed agonists-antagonists) and any modulators capable of blocking the α3β4 nicotinic receptor binding activity. The claims are very broad due to the vast number of possible compounds of that are described as being "α3β4 nicotinic receptor antagonist". The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.), cert. Denied, 02 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for date in the future.(The length of the claimed peptide ranges from 7 amino acid residues to 68 amino acid residues in length. For claim 1, only 2 residues of the maximum 68 residues are disclosed. The limiting claims that limit the length of the peptide claims still claim peptides only disclose up to four amino acid resides.)

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fishcher, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of an antagonist of $\alpha 3\beta 4$ nicotinic receptors is insufficient for enablement. The specification provides no guidance, in the way of enablement for the entire scope of $\alpha 3\beta 4$ nicotinic receptor antagonist other than mecamylaine, 18-methoxycoronaridine, bupropion, dextromethorphan and dextrorphan. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreschfiedl, 110 F. 2d 235, 45 USPQ 36 (CCPA 1940), vies this general rule: "it is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient

number of the members of a group or by other appropriate language, that the chemicals or chemical combination included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S.5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses $\alpha 3\beta 4$ nicotinic receptor antagonists. However, the instant specification only has enablement for mecamylaine, 18-methoxycoronaridine, bupropion, dextromethorphan and dextrorphan.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of $\alpha 3\beta 4$ nicotinic receptor antagonists as that would be enabled in this specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 21-26, 28, 32-34 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glick et al. (Brian Research 719 (1996) 29-35) in view of Pulvirenti et al. (European Journal of Pharmacology 321 (1997) 279-283).

Glick teaches or suggests the use of 18-Methoxycoronaridine for treating of an addiction disorder such as cocaine addiction (abstract; discussion).

Pulvirenti teaches or suggests the use of Dextromethorphan for treating of an addiction disorder such as cocaine addiction (abstract; discussion).

The teaching of Glick differs from the claimed invention in (i) the combination use of 18-methoxycoronaridine and dextromethorphan; (ii) the specific ratio of each active ingredient in a composition; (iii) the preparation of said composition in different dosage forms (e.g., tablet, capsule, granular dispersible power, etc...); and (iv) the incorporation of excipients such as inert diluent, a granulating agent, a disintergrating agent and a lubricating agent when said composition is prepared in the form of a table or capsule. To incorporate such teaching into the teaching of Glick, would have been obvious in view of Pulvirenti who teaches or suggests the use of dextromethorphan for treating of cocaine addiction.

Above references in combination make clear that 18-methoxycoronaridine and dextromethorphan have been individually used for the treatment of cocaine addiction. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).* One having ordinary skill in the art would have been motivated to combine both references such that 18-methoxycoronaridine and dextromethorphan combination would provide more enhanced pharmacological activity in treating cocaine addiction.

Applicant has presented no evidence to establish the unexpected or unobvious nature of the claimed invention, and as such, claims 21-26, 28, 32-34 and 46 are properly rejected under 35 U.S.C. 103.

Conclusion

7. No Claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (703) 308-5377. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax number for this Group is (703) 308-4556.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brian Kwon

ZOHREH FAY
PRIMARY EXAMINER
GROUP 1600